UNITED STATES DEPARTMENT OF COMMERCE
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/187,768	11/06/98	CINCOTTA A	2991/1B206-U

HM12/0912

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EXAMINER	
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ART UNIT	**PAPER NUMBER**
1642	11

DATE MAILED: 09/12/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trad marks

PTO-90C (Rev. 2/95)

1- File Copy

U.S. G.P.O. 2000 ; 465-188/25266

Office Action Summary	Application No.	Applicant(s)	
	09/187,768	CINCOTTA ET AL.	
	Examiner	Art Unit	
	Gary B. Nickol Ph.D.	1642	

-- The MAILING DATE of this communication app ars on the cover sheet with th correspondence address --

Period f r Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).

Status

1)☒ Responsive to communication(s) filed on *19 June 2000* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disp sition of Claims

4)☒ Claim(s) *34-58* is/are pending in the application.

4a) Of the above claim(s) *55-58* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *34-54* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a)☐ All b)☐ Some * c)☐ None of the CERTIFIED copies of the priority documents have been:

1.☐ received.

2.☐ received in Application No. (Series Code / Serial Number) _____ .

3.☐ received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. & 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)
16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *6* .
18) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other: .

DETAILED ACTION

The Election filed June 19, 2000 (Paper No. 10) in response to the Office Action of November 17, 1999 is acknowledged and has been entered. Claims 34-58 are pending in the application and Claims 55-58 have been withdrawn from further consideration by the examiner under 37 CFR 1.142(b) as being drawn to non-elected inventions. Claims 34-54 are currently under prosecution.

Applicant's election with traverse of Group I, claims 34-54 in Paper No 10 is acknowledged. The traversal is on the ground(s) that a careful search would develop the prior art relevant to the claims of Groups I, II, and III. This is not found persuasive. The inventions are classified differently, necessitating different searches in the US Patent shoes. Further, classification of subject matter is merely one indication of the burdensome nature of the search involved. The literature search, particularly relevant in this art, is not coextensive and is much more important in evaluating the burden of search. Different searches and issues are involved in the examination of each group. For these reasons the restriction requirement is deemed to be proper and is therefore made FINAL.

Specification

The specification on page 1 should be amended to reflect the priority status of the present application, for example:

This application claims benefit to provisional application 60/016619, filed May 1, 1996, now abandoned.

The specification is further objected for the following informalities on page 5: Recitation of U.S. Serial No. 07/995,292 is improper since it is should properly reflect the status which is now US Patent No. 5,585,347. Recitation of 08/264,558, is improper and should be removed because this application has been abandoned.

Claim Objections

Claim 38 objected to because of the following informalities: Claim 38 recites "asbout" which appears to be a spelling or grammatical error. Appropriate correction is required.

Claim 48 is objected to because it appears to be a substantial duplicate of Claim 43. Appropriate correction is required.

Claims 54 is objected to because it depends from Claim 48- which as cited above- appears to be a substantial duplicate of Claim 43. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 34-54 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 34-54 are rejected as indefinite as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. While all of the technical details of the method need not be recited, the claims should include enough information to clearly and accurately describe the invention and how it is practiced. In the instant case, Claim 34 has no correlation step clearly reflective of the preamble of the claim.

Claims 43-48 are rejected as vague and indefinite for reciting "benzophenoxazine analogs". The specification does not define what an analog of benzophenoxazine is, and it does not have an art-recognized meaning. Moreover, the definition on page 12 of the specification is not limiting.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 34-54 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for arresting the growth of or eradicating tumors in a human mammal bearing one or more tumors comprising the steps of; administering a prolactin enhancer to said mammal; contacting the cells of said tumor with a photsensistizer; and exposing said

contacted tumor cells to light; wherein said phostosensitizer is a benzophenoxazine analog selected from the group consisting of 5-ethylamino-9-diethylamino-2-iodobenzo[a]phenothiaziniumchloride (EtNBS) or 5-ethylamino-9-diethylamino-benzo[a]phenothiaziniumchloride, does not reasonably provide enablement for treating cancer via photodynamic therapy with any and all benzophenoxazine analogs. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in *Ex parte* Forman, 230 USPQ 546 (BPAI 1986). They include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed.

The claims are broadly drawn to a method for arresting the growth of or eradicating tumors in a human mammal via photodynamic therapy employing a photosensistizer selected from the group consisting of benzophenoxazine analogs (Claims 35-48)

This includes any and all benzophenoxazine analogs.

The specification teaches that benzophenoxazine analogs include benzophenoxazines, benzophenothiazines, and benzophenoselenazines (page 12, line 7). However, such a definition does not specifically define what is included or excluded as a benzophenoxazine analog and such a definition is not limiting. Furthermore, the specification teaches that the photosensitizer is

preferably 5-ethylamino-9-diethylamino-2-iodobenzo[a]phenothiaziniumchloride where administration can be via an intravenous or subcutaneous route (page 24, line 25).

Thus, one cannot extrapolate the teachings of the specification to the scope of the claims because the claims are broadly drawn to any all benzophenoxazine analogs, including those yet to be discovered. Reasonable correlation must exist between the scope of the claims and the scope of enablement set forth, and it cannot be predicted that any and all benzophenoxazine analogs, including those yet to be discovered, could be made and or used to successfully treat tumors in photodynamic therapy. Thus, in view of the lack of predictability and breadth of the claims, it would require undue experimentation for one of relative skill in the art to practice the invention as claimed.

Claims 34-54 are further rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for arresting the growth of or eradicating mammary tumors that do not overexpress prolactin enhancers, does not reasonably provide enablement for a method for arresting the growth of or eradicating tumors in a mammal bearing one or more tumors. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The claims are broadly drawn to a method for arresting the growth of or eradicating tumors in a mammal bearing one or more tumors comprising the steps of: administering a prolactin enhancer to said mammal; contacting the cells of said tumor with a photosensitizer; and exposing said contacted tumor cells to light, wherein said tumor bearing mammal is a human.

This includes a method of arresting the growth of or eradicating any and all types of tumors including those tumors which overexpress prolactin enhancers.

The specification teaches that the photodynamic therapy of the present invention can be used to treat all types of cancers including, but not limited to, papillary bladder tumors, lung cancer, esophageal tumors, gastric, colon , and cervical cancer (page 9, line 20, page 15, line 18). As an example, the specification teaches arresting tumor growth in vivo in mice carrying a murine mammary sarcoma (page 28, line 8). However, it would not be predictable that all tumors would be responsive to PDT and neuroendocrine resetting because there are several instances where tumors actively secrete prolactin enhancers. For example, Bergh et al. (N. Engl. J. Med, 1979, v300 (24), Abstract only) teach bromocriptine in the treatment of prolactinomas. Furthermore, the specification does not teach, what effects, if any, PDT and neuroendocrine resetting would have on hormone sensitive tumors, such as breast and prostate. The specification merely indicates that humans with solid tumors, such as found in breast cancer and prostate cancer, have perturbed prolactin rhythms (page 16, lines 1-5)- and infers that hormonal resetting of the circadian plasma prolactin rhythm will augment PDT in all types of tumors including breast and prostate.

Thus, one cannot extrapolate the teachings of the specification to the scope of the claims because the claims are broadly drawn to the treatment of all types of cancer, including those that overexpress prolactin enhancers and those that are hormonally sensitive. Thus, it would not be predictable that the claimed method would successfully eradicate all types of tumors because it would not be beneficial to treat such tumors with prolactin enhancers if such tumors are already overexpressing prolactin enhancers.

Thus, in view of the lack of predictability and breadth of the claims, it would require undue experimentation for one of relative skill in the art to practice the invention as claimed.

Claims 34-54 are further rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of arresting the growth of or eradicating tumors in a human mammal bearing one or more tumors comprising the steps of; administering a prolactin enhancer to said mammal; contacting the cells of said tumor with a photsensistizer; and exposing said contacted tumor cells to light; wherein said prolactin enhancer is administered at a time between 19:00 and 1:00, does not reasonably provide enablement for a method of treating cancer via photodynamic therapy with a prolactin enhancer at any time. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The claims are broadly drawn to the treatment of cancer via photodynamic therapy using a prolactin enhancer at any time (Claims 34-39,43-45).

The specification teaches that administration of prolactin enhancers is inhibitory to tumor growth in mammals when given at time intervals during a 24 hour period which correspond to the peak of prolactin secretion in healthy mammals (page 14, lines 16-18). The same time restraint is taught with the administration of melatonin wherein administration of melatonin at the time during a 24-hour period when melatonin levels are peaking exerts a potent inhibitory effect on growth of tumors (page 15). Further, the specification teaches administration of prolactin, "at the appropriate time interval", in combination with PDT resulted in a near 100% tumor cure (page 27, lines 18-20). Thus, it appears that the "time" of prolactin enhancer

administration in conjunction with PDT therapy is critical to tumor response rates. In fact, successful reduction in tumor burden occurred when either prolactin or melatinon was administered at 10 hours after light onset when combined with PDT (Examples 1 and 5).

Thus, one cannot extrapolate the teachings of the specification to the scope of the claims because the claims are broadly drawn to the treatment of cancer with PDT in combination with a prolactin enhancer which is administered at any time during a 24 hour period. Based on the disclosure, there is insufficient guidance and objective evidence to insure undue experimentation in the successful treatment of cancer when prolactin enhancers are administered at any time during a 24 hour period in combination with PDT. Reasonable correlation must exist between the scope of the claims and the scope of enablement set forth, and it cannot be predicted that such a method would arrest or eradicate tumors in a human when prolactin enhancers are administered at any time of the day.

Thus, in view of the lack of predictability and breadth of the claims, it would require undue experimentation for one of relative skill in the art to practice the invention as claimed.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 34 is rejected under 35 U.S.C. 102(a) as being anticipated by Werning et al. (Arch. Ontolaryngol. Head Neck Surg., July 1995, v121, pp. 783-789, IDS) as evidenced by Molitch, ME. (Endocrinol.Metab.Clin.North.Am, 1992, v21(4), ABSTRACT only).

Claim 34 is drawn to a method for arresting the growth of or eradicating tumors in a mammal bearing one or more tumors comprising the steps of: administering a prolactin enhancer to said mammal; contacting the cells of said tumor with a photosensitizer; and exposing said contacted tumor cells to light.

Werning et al. teach a method of arresting the growth of or eradicating tumors in a mammal bearing one or more tumors comprising the steps of administering a prolactin enhancer (metoclopramide) to said mammal; contacting the cells with a photosensitizer; and exposing said contacted tumor cells to light (see abstract). Metoclopramide, as evidenced by Molitch, ME is a prolactin enhancer.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 34-36, 43 are rejected under 35 U.S.C. 103(a) as being unpatentable over Werning et al. (Arch. Ontolaryngol. Head Neck Surg., July 1995, v121, pp. 783-789, IDS) and Molitch, ME. (Endocrinol.Metab.Clin.North.Am, 1992, v21(4), ABSTRACT only).

The claims are drawn to a method for arresting the growth of or eradicating tumors in a mammal bearing one or more tumors comprising the steps of: administering a prolactin enhancer to said mammal; contacting the cells of said tumor with a photosensitizer; and exposing said contacted tumor cells to light (Claim 34), wherein said tumor bearing mammal is a human (Claim 35), wherein said prolactin ehancer is a member selected from the group consisting of prolactin, melatonin, metoclopramide, domperidione, 5-hydroxytryptophan, and pharmaceutically acceptable salts thereof (Claim 36), wherein said photosensitizer is selected from the group consisting of porphyrin dyes, phthalocyanine dyes, cyanine dyes, benzophenoxazine analogs, and pharmaceutically acceptable salts thereof (Claim 43).

1. Werning et al. and Molitch, ME teach as set forth above. Werning et al. further teach a photosensitizer selected from the group consisting of phthalocyanine dyes (2nd paragraph, page 783).
2. Werning et al. does not specifically teach such a method of eradicating tumors in humans.

However, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to alter the method of Werning et al. so as to include the treatment of a human mammal bearing a tumor. Such a transition to humans is obvious, and one would have been motivated to do so, because Werning et al. teach a tumor model comparable to the human situation (page 788, 1st column) which resulted in a "complete cure" (page 788, 2nd column, 2nd paragraph) (abstract, see results).

Claims 34-54 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lissoni et al. (Cancer, 1994, v73(3), pp.699-701, IDS) and Bartsch et al. (Ann. NY Acad. Science, 1994, v719, pp. 502-525, IDS) in view of Cincotta et al. (Cancer Research, 1994, v54, pp. 1249-1258, IDS) and Cincotta et al. (Cancer Research, 1993, v53. Pp. 2571-2579).

The claims are drawn to a method for arresting the growth of or eradicating tumors in a mammal bearing one or more tumors comprising the steps of: administering a prolactin enhancer to said mammal; contacting the cells of said tumor with a photosensitizer; and exposing said contacted tumor cells to light (Claim 34), wherein said tumor bearing mammal is a human (Claim 35), wherein said prolactin enhancer is selected from the group consisting of prolactin,

melatonin, metoclopramide, domperidione, 5-hydroxytryptophan, and pharmaceutically acceptable salts thereof (Claim 36); wherein said prolactin enhancer is melatonin or a pharmaceutically acceptable salt thereof (Claim 37); wherein said melatonin or a pharmaceutically acceptable salt thereof is administered in an amount within the range of about 0.5 to about 20 mg/person/day(Claim 38); wherein said prolactin ehancer is administered at a time between about 19:00 and 1:00 (Claims 40-42); wherein said prolactin enhancer is prolactin (Claim 39);wherein said photosensitizer is selected from the group consisting of porphyrin dyes, phthalocyanine dyes, cyanine dyes, benzophenoxazine analogs, and pharmaceutically acceptable salts thereof (Claims 43-48) wherein said benzophenoxazine analog is a member selected from the group consisting of 5-ethylamino-9-diethylamino-2-iodobenzo[a]phenothiaziniumchloride and 5-ethylamino-9-diethylamino-2-benzo[a]phenothiaziniumchloride (Claims 49-54).

1. Lissoni et al. teach a method of arresting the growth of or eradicating tumors in human mammals by administration of melatonin at about 20mg/person/day between about 19:00 and 1:00. Lissoni et al. do not teach a method of combining melatonin and photodynamic therapy for the treatment of tumors.
2. Bartsch et al. teach that melatonin is a prolactin enhancer (page 514, 2nd paragraph) and that melatonin, as an adjuvant or substitute to other therapies, may help to prevent if not to restore central endocrine imbalances in cancer patients with depressed melatonin (page 521, last paragraph). Bartsch et al. do not specifically teach a method of combining melatonin and photodynamic therapy for the treatment of tumors.

3. Cincotta et al (Cancer Res., 1994, 54:1249-1258) teaches that 5-ethylamino-9-diethylamino-benzo[a]phenothiazinium chloride (EtNBS) is a photosensitizing agent and teach a method of treating tumors in a mammal with EtNBS and that photodynamic therapy of EMT-6 tumors in mice with the 5-ethylamino-9-diethylamino-benzo[a]phenothiazinium chloride (7.5 mg of dye/kg, 50 mWatts/cm^2 and 100 joules/cm^2) resulted in direct tumor cell killing rather than destruction of the supporting vasculature and that (a) maximum uptake of the dye in tissue and (b) discrimination between tumor and skin or muscle occurred at 3-8 h after sc injection of the 5-ethylamino-9-diethylamino-benzo[a]phenothiazinium chloride (see Abstract). Further, the dye has attributes beneficial for the treatment of malignant disorders including (a) a high degree of lipophilicity, (b) rapid intracellular accumulation and (c) efficient absorption of light in a spectral region where light penetrates tissue maximally.
4. Cincotta et al. (Cancer Research, 1993, v53. Pp. 2571-2579) teach that 5-ethylamino-9-diethylamino-benzo[a]phenothiazinium chloride is a benzophenoxazine analog (see abstract and title).
5. It is well-known in the art that prolactin is a prolactin enhancer- as evidenced by Molitch, ME. (Endocrinol.Metab.Clin.North.Am, 1992, v21(4), ABSTRACT only).

Neither Cinotta et al. (both references) nor Bartsch et al. and Lissoni et al. teach a method for treating tumors by combining melatonin and photodynamic therapy for the treatment of tumors. However, in the absence of unexpected results, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of the references and to treat tumors with both of these methods together. Each of these methods had been taught by the prior art to successfully treat tumors. Clearly, the instant situation is

amenable to the type of analysis set forth in In re Kerkhoven, 205 USPQ 1069 (CCPA 1980) wherein the court held that it is *prima facie* obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose in order to produce a third composition that is to be used for the very same purpose since the idea of combining them flows logically from their having been individually taught in the prior art. Applying the same logic to the instant method claims, given the teaching of the prior art of methods for treating tumors using each of the claimed compositions, it would have been obvious to treat a mammal with both a photosensitizer and melatonin because the idea of doing so would have logically followed from their having been individually taught in the prior art to be useful for the same purpose, that is, for the treatment of tumors. Thus, one of ordinary skill in the art would have reasonably expected to successfully treat tumors with either or both of these compositions since both had been demonstrated in the prior art to successfully treat tumors. Finally, it would have been *prima facie* obvious to one of ordinary skill in the art to substitute melatonin as taught by Lissoni et al with prolactin since prolactin is known to be a prolactin enhancer and are therefore functional equivalents. Further, one would have been motivated to do so since administration of prolactin resulted in the inhibition of mammary tumors appearance in prolactinized rats as evidenced by Nagasawa et al. – see abstract and Table 1 (Cancer Res., 1974, v34. Pp. 2643-2646).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gary B. Nickol Ph.D. whose telephone number is 703-305-7143. The examiner can normally be reached on M-F, 8:30-5:00 P.M..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa can be reached on 703-308-3995. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Gary B. Nickol, Ph.D.
Examiner
Art Unit 1642

GBN
September 7, 2000

Susan Ungar

SUSAN UNGAR, PH.D
PRIMARY EXAMINER